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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/615,854	07/14/2000	Keith L. Black	CEDAR-044569	4523

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EXAMINER	
QIAN, CELINE X	
ART UNIT	PAPER NUMBER
1636	8

DATE MAILED: 05/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n N .	Applicant(s)	
	09/615,854	BLACK ET AL.	
	Examiner	Art Unit	
	Celine Qian	1636	

-- Th MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-10,12-24,48-55,57-71,135-144 and 146-160* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12-24,48-55,57-71,135-144 and 146-160* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-10, 12-24, 48-55, 57-71, 135-144 and 146-160 are pending in the application.

Election/Restrictions

Applicant's election without traverse of Group I in Paper No. 7 is acknowledged. Accordingly, claims 11, 25-47, 56, 72-134, 145 and 161 are canceled. Claims 1-10, 12-24, 48-55, 135-144 and 146-160 are currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 12-24, 48-55, 57-71, 135-144 and 146-160 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of delivering a medicament that is transported by Ca dependent K channel to a glioma or ischemia region in the brain of a mammalian subject by administering a effective amount of NONOate compound (a group of soluble guanylyl cyclase activator belong to nitric oxide donor subclass) simultaneously with the medicament, does not reasonably provide enablement for a method of delivering any medicament to any kind of abnormal brain region by administering any potassium channel activator. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The nature of the invention is a method of delivering a medicament to an abnormal brain region in a mammalian subject by administering a K channel activator simultaneously with the medicament, wherein the K channel activator belongs to the soluble guanylyl cyclase activator group. The inventions also encompass a pharmaceutical composition comprising said K channel activator formulated in a pharmaceutically acceptable solution together with a medicament for delivery by intra-vascular infusion or injection into a mammal, and a kit comprising said K channel activator for enhancement of a medicament delivery to an abnormal brain region or a tumor.

The specification discloses that by administering NS 1619, YC-1, DEA/NO or PAPA/NO (all of which are Ca dependent K channel activator), at a concentration of 39.9 μg/kg, to a rat bearing implanted glioma tumor cells (RG2), the permeability of the Ca activated K channel increases in capillaries of the malignant tumor (see page 29, lines 18-31, page 30, lines 1-14). The specification also discloses that K channel activator NS-1619 and nitric oxide donor increases the permeability to the ischemic rat brain region induced by MCA occlusion (see page 33-34). The specification further discloses that the density and total area of the pinocytotic vesicles increased in tumors after bradykinin and NS-1619 treatment comparing to the normal area (see page 33, Table 1), implying transendothelial vesicular transport is a primary cellular mechanism for drug delivery to the tumor cells (see page 33, lines 21-23 and 30-31).

The state of the art at the time of filing does not teach a method of enhanced delivery of any medicament to an abnormal brain region by administering any kind of K channel activator simultaneously with the medicament. Therefore, one skilled in the art would have turn to specification for guidance to practice the claimed inventions.

The breath of the claims is very broad. The broadest claim is drawn to a method of delivering any kind of medicament, ranging from nucleic acids, proteins, organic or inorganic chemical compounds, and diagnostic agents, to any part of the brain having abnormal feature(s). The claim also encompasses any kind of K channel activator that activates soluble guanylyl cyclase.

However, the guidance presented in the specification is very limited. The specification only teaches that by administering NS 1619, YC-1, DEA/NO or PAPA/NO (at a concentration of 39.9 μg/kg) to a rat bearing implanted glioma tumor (RG2), the permeability of the Ca activated K channel increases in capillaries of the malignant tumor (see page 29, lines 18-31, page 30, lines 1-14). The specification also teaches that K channel activator NS-1619 and nitric oxide donor with increases the permeability to the ischemic rat brain region induced by MCA occlusion (see page 33-34). The specification fails to demonstrate whether administering K channel activators as mentioned above to other types of brain injuries including trauma, infection and stroke (as claimed in claim 2) would increase permeability to a medicament comparing to the normal brain region. The specification also fails to show whether administering K channel activator to other types of tumor or tumors in other areas (as claimed in claims 3, 57 and 58) would increase permeability to any kind of medicament. The state of art at the time of filing does not teach that brain injuries of other types or tumors of other types would result in increased expression of Ca dependent K channels. In 2001, a year after the filing date, there is only one report that teaches human glioma cells highly express Ca dependent K channel (see Ransom and Sontheimer 2001, Journal of Neurophysiology, vol.85: 790-803). Therefore, administering K channel activator to enhance the delivery of a medicament to any type of tumor (except glioma

as shown by the specification) or any type of brain injury (except ischemia) is not well recognized in the art and unpredictable.

Soluble guanylyl cyclase catalyzes the conversion of intracellular GTP to cyclic GMP, an important second messenger that is involved in many cellular events, including the regulation of Ca dependent K channel. This enzyme is activated by the binding of compounds such as YC-1, nitric oxide or nitric oxide (NO) donors.

There are five classes of nitric oxide donor including organic nitrate compounds, iron nitrosyl compounds, S-nitrosothiol compounds, sydnonimine compounds and NONOate compounds (see Feelisch 1998, Naunyn-Schmiedeberg's Arch Pharmacology, 358: 113-122). Although all NO donors somehow produce NO-related activity when applied in biological systems, several factors affect their biological action: 1) the pathways leading to NO formation, such as enzymatic or non-enzymatic production and dependence on thiol or oxygen (see page 114, lines 1-4, and Table 1). 2) the total amount of NO generated from each of those compound determines the quality and magnitude of the biological response (see page 114, col.1, 2nd paragraph lines 1-6). 3) the redox state of the NO-related species released from each compound determines the final amount of NO generated (see page 114, 2nd col. 1st paragraph). 4) The effective amount of each of those compound used in vitro versus in vivo. These factors not only affect the effectiveness of each of those compound in a given biological system, they also affect the route of administration of said compound. For example, short-lived NO donors may have to be administered as continuous infusion rather than bolus form in order to avoid the delivery of only a short burst of NO (see page 114, 1st col. 2nd paragraph, lines 6-9).

The tissue specificity can also affect the effectiveness of those compounds because the extent of conversion of some of those compounds to NO would also depend on enzymatic profile of the tissue or organ. To add to the complexity, the biological effects generated by some of those compounds are not entirely mediated by NO but other metabolites or decomposition product (see page 118, 1st col. 3rd paragraph, lines 18-21). Although the specification discloses that four different soluble guanylyl cyclase activators (including two nitric oxide donor) increases permeability (through increased K channel conductance) to tumor and ischemic region of the rat brain, as Feelisch indicates that "the selection of these compound (for experiments or treatments) is not a trivial issue," the method for delivering a medicament to an abnormal brain region using any of those compounds as claimed is unpredictable. Especially because some of the NO donors cause "coronary steal," an unfavorable redistribution of blood away form ischemic region (see page 115, 1st col., lines 2-3). This further complicates the method of delivering a medicament to an ischemic region in brain as the compound itself would worsen the ischemic condition.

The method of enhancing delivery to an abnormal brain region of any medicament including DNA, protein and chemical by administering a K channel activator is also unpredictable. The specification discloses that transendothelial vesicular transport is a primary cellular mechanism for drug delivery to the tumor cells. However, not all the medicament delivery is through transendothelial vesicular transport or through Ca dependent K channel. For example, some molecules may utilize ATP dependent K channel or by simple diffusion. On the other hand, viral vectors need to utilize cell surface receptors to infect the cells. Therefore, the mere demonstration of increased permeability in tumor or ischemic brain region to horse radish

peroxidase, Evan blue or α-aminoisobutyric acid does not render the increased permeability to other medicament or diagnostic agent obvious. Thus, the method of enhance delivery to an abnormal brain region of any medicament by administering a K channel activator is unpredictable.

The inventions also encompass a very broad range of the dosage of K channel activator used in the method, with the broadest claim (21 and 68) ranging from 0.075 to 1500 μg/kg body mass. However, the specification discloses the effective dose for the compounds used is between 40-80 μg/kg (2.66 and 5.3μg/kg/min for 15min). Therefore, whether the dosage as low as 0.075 or as high as 1500 μg/kg is effective in the method of enhancing medicament delivery to an abnormal brain region is unpredictable. In fact, as Feelisch indicates that "the vasodilator properties of classical NO donors limit their potential usefulness in non-cardiovascular applications where lowering of systemic blood pressure often represents an unwanted side effect" (page 114, 2nd col. 3rd paragraph, lines 9-12). In addition, in many cases, effects obtained with comparatively high doses of NO donors are opposite to those observed at lower doses (see page 115, 1st paragraph, last 6 lines). The method of delivering a medicament to an abnormal brain region by administering a K channel activator at dosage ranging from 0.075-1500, 150, 100 or 15 μg/kg is unpredictable.

In view of the factors discussed above that renders the invention unpredictable, one skilled in the art would have to turn to art or specification for guidance to practice the invention. However, the prior art does not teach a method of delivering medicament to an abnormal brain region by administering K channel activator. The specification fails to provide guidance to overcome the problems that render the inventions unpredictable. Therefore, one skill in the art

would require undue amount of experimentation to practice the claimed invention commensurate in scope with these claims.

Claims 1-10, 12-24, 48-55, 57-71, 135-144 and 146-160 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite "administering to a mammalian subject ... a potassium channel activator, said potassium activator being an activator of soluble guanylyl cyclase." The specification discloses six K channel activators (NS1619, minoxidil sulfate, bradykinin, YC-1, DEA/NO and PAPA/NO) that increase the permeability of blood tumor barrier. However, not all of the K channel activators are also activators of soluble guanylyl cyclase. For example, minoxidil sulfate activates K[ATP] channel instead of Ca dependent K channel that is responsive to cyclic GMP regulation. The specification fails to describe a structure/function relationship between K channel activators that also activates soluble guanylyl cyclase, for instance, what common structures or characteristics that are shared by those compounds which allow them to activate both K channel and soluble guanylyl cyclase? However, applicants are broadly claiming any K channel activator being an activator of soluble guanylyl cyclase. Therefore, the specification fails to describe the claimed subject matter in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10, 12-24, 48-55, 57-71, 135-144 and 146-160 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 1-10, 12-24, 48-55, 57-71, 135-144 and 146-160, the word "medicant" renders the claim indefinite because the word has no meaning. It appears to be a mis-spelling for the word "medicament." Amending the claim as such would obviate this rejection.

Regarding claims 1-10, 12-24, 48-55 and 57-71, the term "substantially simultaneously" renders the claim indefinite because it is unclear whether it is simultaneous or not. As such, the metes and bounds of the claims cannot be established.

Regarding claims 17, 64 and 150, the word "derived" renders the claims indefinite because the nature and derivative process is not known. As such, the metes and bounds of the claims cannot be established.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
May 6, 2002

REMY YUCEL, PH.D
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